increase the viability of embryos cultured therein; and (3) present references showing that the common wisdom in the field of embryology at the time of the invention taught away from the use of recombinant human albumin as a substitute for serum-derived albumin in embryo culture media. As discussed in detail below, Applicants have complied with each of the aforementioned suggestion.

In view of the following remarks, reconsideration and withdrawal of the rejections to the application in the Office Action is respectfully requested.

I. Rejection of Claims Under 35 U.S.C. § 112 Second Paragraph

In the Office Action claims 6, 10-20 and 26-33 were rejected under 35 U.S.C. § 112, second paragraph, for being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, claims 6, 10, 17, 26, 30 and 33 were rejected because they include the phrase "capable of." According to the Office Action, this phrase renders the claims indefinite because it is unclear if the media actually increases the viability of the gametes or embryonic cells cultured in the medium or if the media is merely capable of increasing the viability of the cells. Claims 6, 10, 26, 30 and 33 have been amended to clarify that the medium actually increases the viability of gametes or embryonic cells cultured in the medium. Claim 17 has been canceled. Applicants believe that these amendments render the rejected claims definite and respectfully request that this rejection be withdrawn.

II. Rejection of Claims 1-6, 10-20 and 30-33 Under 35 U.S.C. § 103(a)

Claims 1-6, 10-20 and 30-33 were rejected in the Office Action under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,153,582 issued to Skelnick (hereinafter "Skelnick") in view of U.S. Patent No. 5,612,198 issued to Becquart (hereinafter "Becquart") and an article by Kjems.

In support of the rejection, the Examiner characterized Skelnick as follows:

> Skelnick teaches a defined serum-free composition comprising a glycosaminoglycan, such as hyaluronic acid . . . a deturgescent agent, such as albumin . . . and a buffer system, such as sodium citrate . . . in a medium that can support cell development, here MEM, TC199, or HTF. Skelnick also teaches that non-human derived serum contains many substances capable of eliciting an immune response.

> Skelnick does not explicitly teach that the albumin used is recombinant human albumin.

With regard to Becquart, the Examiner further stated:

> Becquart teaches a recombinant human albumin which possesses all of the properties of human albumin extracted from sera (see col. 3, lines 11-14). Becquart teaches that recombinantly producing human albumin removes the risk of viral contamination (see col. 1, lines 53-57) and greatly lowers the risk of immunogenic reactions when used in pharmaceutical applications (see col. 3, lines 47-49).

Based on these teachings, the Examiner asserts it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the media of Skelnick by substituting the recombinant human albumin of Becquart to create a supplement that is free of non-recombinant human albumin. Applicants respectfully traverse.

In order to establish a prima facie case of obviousness, the cited references, alone or in combination, must teach or suggest all of limitations of the rejected claims. The cited references fail to render the claimed invention obvious because they fail to teach a cell culture medium that increases the viability of gametes or embryonic cells cultured therein. This argument was presented by Applicants in the Amendment and Request for Reconsideration Under 37 C.F.R. § 1.111 mailed March 17, 2003 in response to the previous Office Action. In response the Examiner stated:

> Furthermore, increasing the viability of gametes or embryos is considered to be an intended use for the media. It is respectfully pointed out that a recitation of the intended use of the claimed invention (here, the culture media/supplement) must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. . . . Without a clear indication that the claimed media is structurally different from the media made by combining the cited references, both media would be capable of performing the intended use (increasing viability).

Skelnick teaches a serum-free medium for use in the preservation of corneal tissue. The medium of Skelnick includes components selected from sixteen different groups, as outlined at column 3, line 52 through column 4, line 55. The sixteen groups are labeled (a) through (p) in claim 1 of Skelnick. Components of group (i) are ATP and energy precursors.

Examples of group (i) components are provided in column 4, lines 14-17. Components of group (k) are co-enzymes and enzyme supplements. Examples of group (k) components are provided in column 4, lines 27-29. Components of group (l) are nucleotide precursors. Examples of group (l) components are provided in column 4, lines 30-33. Components of group (o) are trace minerals and trace elements. Examples of group (o) components are provided in column 4, lines 39-44. As one of ordinary skill in the art would recognize, components (i), (k), (l), and (o) of the medium taught by Skelnick would inhibit the growth any embryos cultured in that medium. This is demonstrated by the experimental data presented in the accompanying declaration of David K. Gardner. These data show that embryos cultured in a corneal preservation medium made substantially as described in Skelnick failed to survive past a 1-cell development stage. Therefore, Skelnick does not teach a culture medium that increases the viability of gametes or embryonic cells cultured therein, as recited in the rejected claim. For this reason Applicants respectfully request that this rejection be withdrawn.

Finally, with respect to claims 30 and 33, Applicants draw the Examiner's attention to the transition phrase "consisting essentially of." This partially closed transition language limits the claims to compositions containing the elements specifically listed therein and those materials that do not materially affect the basic and novel characteristics of the claimed invention. (MPEP § 2111.03) One of the basic and novel characteristics of the mammalian culture media recited in rejected claims 30 and 33 is that those media include recombinant human albumin and are capable of increasing the viability of gametes or embryonic cells cultured therein. As discussed in the accompanying declarations of K. Gardner, the compositions described in Skelnick are incapable of increasing the viability of gametes or embryonic cells cultured therein. Therefore, the compositions of Skelnick include components that materially affect the basic and novel characteristics of the claimed mammalian cell culture media. For this reason, the teachings of Skelnick do not render claims 30 and 33 unpatentable.

III. Rejection of Claims 1-20 and 30-33 Under 35 U.S.C. § 103(a)

In the Office Action, claims 1-20 and 30-33 were rejected under 35 U.S.C. § 103(a) as being unpatentable over United States Patent No. 6,140,121 issued to Ellington et al. (hereinafter "Ellington") in view of Becquart and Kjems and further in view of Skelnick. In support of this rejection, the Examiner stated:

> Ellington teaches a medium such as Ham's F-10 Earl's, Whitten's or PBS for culturing sperm, embryos or embryonic stem cells (see col. 16, lines 13-19) comprising a macromolecule, a buffer, as well as a protein (see col. 16, lines 25-35). Ellington teaches that the macromolecule can be hyaluronic acid (see col. 13, lines 56-65), the buffer can be sodium citrate (see col. 16, line 56), and the protein can be human albumin (see col. 16, lines 25-35; and col. 13, lines 56-65).

The Examiner goes on to acknowledge that Ellington does not teach a media comprising recombinant human albumin. However, the Examiner asserts that it would have been obvious to one of ordinary skill in the art to modify the media of Ellington by substituting the serum-derived human albumin with recombinant human albumin based on the teachings of Becquart. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness based on two or more references, the cited references, alone or in combination, must teach all limitations of the rejected claims. In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Finally, any combination or modification of the cited reference must be based on a reasonable expectation of success. (MPEP 2142)

Based on the knowledge generally available at the time of the invention, one of ordinary skill in the art would not reasonably have expected to successfully produce a culture medium that increased the viability of embryos cultured therein by replacing the serum-derived human albumin of Ellington with recombinantly produced human albumin. Prior to the inventors' surprising and unexpected discovery that serum-derives albumen could be replaced by recombinant albumin, the common knowledge in the field of embryology was that various unidentified and poorly understood contaminants associated with the serum-derived albumin played an essential role in promoting the viability of gametes and embryos. Applicants have enclosed five articles that reflect this common knowledge. Each of these articles has been cited in a Supplemental Information Disclosure Statement and accompanying form PTO-1449 filed concurrently with this response.

The first article is an abstract for a presentation at a meeting of the British Society of Animal Science in September 1999. The article, "Effects of Serum or Fatty Acid Supplementation of Synthetic Oviduct Fluid Medium on Development of Bovine Embryos in

Vitro" by Farrar et al., presents studies of serum-containing embryo culture media. The article teaches that culture media which avoid the use of serum-derived albumin are unfavorable due to the lack of knowledge regarding the embryo's response to specific nutrients, such as fatty acids. (See introduction.)

The second article, "Letter to the Editor: Different Lots of Bovine Serum Albumin Inhibit or Stimulate in Vitro Development of Hamster Embyos," Susan H. McKiernan and Barry D. Bavister, In Vitro Cell. Dev. Biol., **28A**, 154-156 (1992), teaches:

> . . . serum albumin, in general, binds biological substances such as fatty acids, steroids and many trace metals, provides an accessible protein reserve, serves as a colloid osmotic regulator and acts as a transport protein. Thus, BSA is not an inert constituent of culture media and may provide low molecular weight growth-promoting factors . . . ." (See column 1, first paragraph.)

The third article, "Oxygen Concentration and Protein Source Affect the Development of Preimplantation Goat Embryos In Vitro," Batt et al., Reprod. Fertil. Dev., **3**, 601-607 (1991), teaches that the protein source used to supplement a culture media affects the development of early goat embryos *in vitro*. The article concludes:

> More than one factor may be responsible for the varying ability of the different protein sources to support development of early goat embryos in vitro. Commercial preparations of serum albumin are contaminated with proteins other than albumin (Peters 1975; Kane and Headon 1980; Batt and Miller 1988a, 1988b), as well as fatty acids and other small molecules (Kane and Headon 1980). These small molecules include an embryotrophic growth factor, which stimulates cell division and growth in rabbit morulae and blastocysts (Kane 1985). (See page 605, first full paragraph.)

The fourth article, "Protein-Free Culture Medium Containing Polyvinylalcohol, Vitamins, and Amino Acids Supports Development of Eight-Cell Hamster Embryos to Hatching Blastocysts," Kane et al., J. Expt. Zoology, **247**, 183-187 (1988), describes the successful hatching of hamster embryos in a cell culture that contains bovine serum albumin but no additional vitamins. The authors attribute the success to the presence of vitamin contaminants associated with the albumin in the culture. (See column 1, second paragraph, page 186.)

The fifth article, "Minimal Nutrient Requirements for Culture of One-Cell Rabbit Embryos," Michael T. Kane, Biology of Reproduction, **37**, 775-778 (1987), reports studies of the cleavage of one-cell rabbit embryos during *in vitro* culture with polyvinylalcohol alone or

combined with bovine serum albumin, amino acids, or one of a number of potential energy sources. The results showed that the addition of the bovine serum albumin produced the greatest increase in the cleavage rate. The authors explained this result as follows:

> Much of this effect probably is due to the presence of low-molecular weight energy substrates, such as fatty acids, etc., which are normally bound to albumin (Fredrickson and Gordon, 1958). (See column 2, second full paragraph, page 777.)

Thus, as reflected in each of the five articles cited above, one of skill in the art would not have expected to successfully produce an embryo culture medium by replacing a serum-derived albumin with a recombinantly derived albumin because such a replacement would have been expected to rob the resulting medium of contaminants essential to the growth of the embryos. For this reason, Applicants respectfully request that this rejection be withdrawn.

Applicants further note that claims 1, 10, 26, 30, and 33 have been amended to include the limitation that the claimed culture media are free from non-recombinant human albumin, as recommended by Examiner Nguyen in our telephone conversation of March 12, 2003. None of the references cited by the Examiner teaches or suggests a culture medium that is free of non-recombinant human albumin. For this additional reason, Applicants respectfully request that this rejection be withdrawn.

With regard to claims 2, 6, 11, 15, 26-29, and 30-33, Applicants further note that each of these claims recites a culture medium that includes citrate. As noted above, the Examiner characterized Ellington as teaching a medium for culturing embryos or embryonic stem cells comprising a buffer, wherein the buffer can be sodium citrate. Applicants respectfully submit that the Examiner has mischaracterized the teachings of Ellington. Ellington teaches various media, some of which are suitable for freezing sperm, oocytes, or embryos and others which are suitable for culturing oocytes and embryos. The Examiner refers to column 16, line 57 of Ellington in support of this rejection. However, the disclosure at column 16, line 57 is specifically directed to a culture medium designed to *freeze* sperm, oocytes, or embryos. Moreover, the cited language actually recommends a sodium citrate buffer only for a sperm freezing medium. Phosphate buffered saline is recommended as the buffer for use in freezing oocytes and embryos. In fact, sodium citrate is only mentioned in Ellington with respect to media for use with sperm. Thus, Ellington, alone or in combination with the other references cited by the Examiner, fails to teach or suggest a culture medium containing citrate that is

capable of increasing the viability of embryos cultured therein. For this reason, Applicants respectfully request that this rejection be withdrawn.

IV. Conclusion

In view of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the pending rejections. If Examiner Angell has any questions, or believes a telephone discussion would expedite the prosecution of this application, he is invited to contact the undersigned.

Respectfully submitted,

Date April 17, 2003

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CLAIM AMENDMENTS

1. A mammalian culture medium supplement comprising recombinant human albumin and fermented hyaluronan, wherein the supplement increases the viability of gametes or embryonic cells cultured in a medium containing the supplement, and further wherein the supplement is free from non-recombinant human albumin.

10. A mammalian culture medium comprising recombinant human albumin and a medium that can support cell development, wherein the mammalian culture medium [is capable of increasing]increases the viability of gametes or embryonic cells cultured in the medium, and further wherein the mammalian culture medium is free from non-recombinant human albumin.

26. A kit for supplementation of mammalian culture medium, comprising:

(a) a medium comprising recombinant human albumin, and optionally one or more ingredients selected from the group consisting of mammalian culture medium, [recombinant human albumin,]fermented hyaluronan, citrate and combinations thereof, wherein the medium [is capable of increasing]increases the viability of gametes or embryonic cells cultured in the medium, and further wherein the medium is free from non-recombinant human albumin; and

(b) instructions for use of the kit.

30. A mammalian culture medium consisting essentially of:

(a) a medium that can support mammalian embryo or cell development;

(b) recombinant human albumin in an amount from about 0.1 mg/ml to about 20.0 mg/ml;

(c) fermented hyaluronan in an amount from about 0.1 mg/ml to about 5.0 mg/ml; and

(d) citrate in a concentration from about 0.1 mM to about 5.0 mM,

wherein the mammalian culture medium [is capable of increasing]increases the viability of gametes or embryonic cells cultured in the medium, and further wherein the mammalian culture medium is free from non-recombinant human albumin.

33. A mammalian culture medium supplement consisting essentially of:

(a) recombinant human albumin in an amount from about 0.125 mg/ml to about 20.0 mg/ml;

(b) fermented hyaluronan in an amount from about 0.1 mg/ml to about 5.0 mg/ml; and

(c) citrate in a concentration from about 0.1 mM to about 5.0 mM,

wherein the mammalian culture medium [is capable of increasing]increases the viability of gametes or embryonic cells cultured in the medium, and further wherein the mammalian culture medium is free from non-recombinant human albumin.